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A DIFFUSION APPROXIMATION ANALYSIS OF A GENERAL N-COMPARTMENT S--ETC(U)
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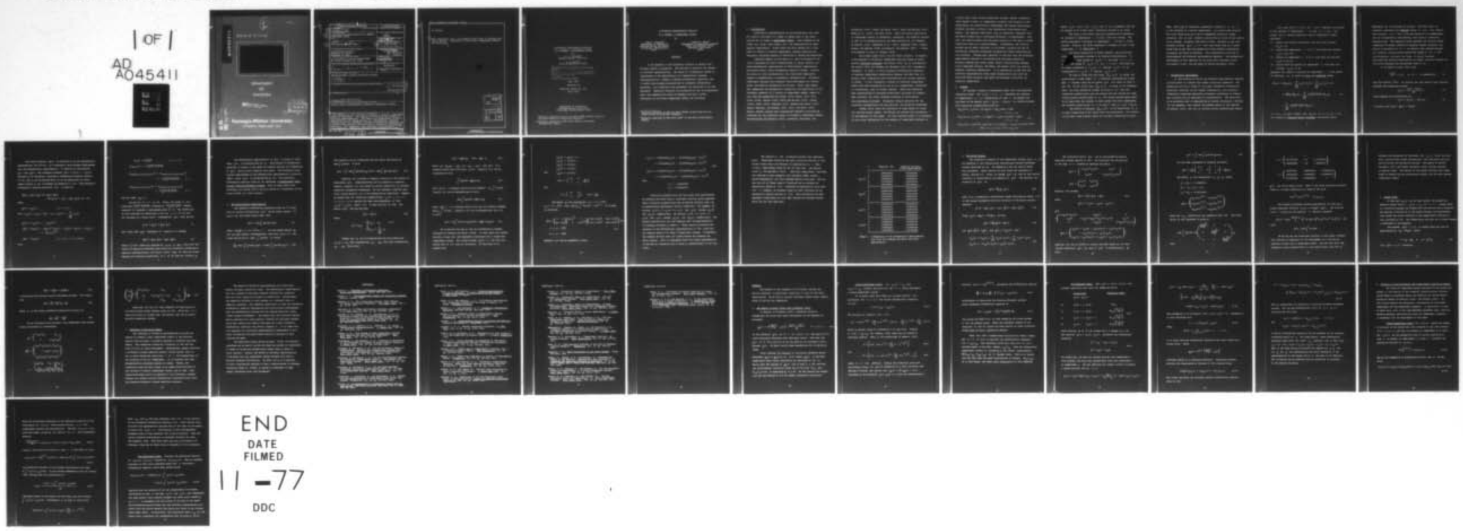

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OF A GENERAL n-COMPARTMENT SYSTEM

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ABSTRACT

A new approach to the stochastic analysis of general compartment models is presented. The analysis is based on the concept of diffusion approximations. The state of a compartment system is represented as the superposition of a deterministic process, characterized by a system of ordinary differential equations, and a random noise process characterized by stochastic differential equations. All transition rate parameters are permitted to be time dependent. Numerical solutions are presented for the two-compartment case, and compared with those of Cardenas and Matis (1975a). Extensions to non-linear compartment models are discussed.

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1. Introduction

Quantitative representation of the distribution over time of a drug or pollutant in a human or animal body is now often carried out in terms of compartment models. Such elements as the blood, gut, liver, lean tissue, etc., are characterized as homogeneous compartments, within which the drug resides for a time, later to transit to another compartment, perhaps recycling but eventually vanishing because of evacuation or metabolism mechanisms.

Classical papers in this area, e.g. that by Bischoff et al. (1971) concerned with use of methotrexate in cancer therapy, proposed deterministic descriptions of flows between compartments, and stocks within, using differential equation systems. However, variations in drug concentrations over replicated experiments suggest a probabilistic or stochastic representation. Stochastic compartment analysis has undergone rapid development for several years, and might be categorized as follows. First, many papers have emphasized the mathematical formulation and exploration of the stochastic behavior of a variety of compartment models; papers of this type are exemplified by Bright (1973), Matis (1972, 1974, 1975a, 1975b), Marcus (1975), Matis and Hartley (1972), Purdue (1974a, 1974b, 1975), Rescigno (1973), Rubinow and Winzer (1971), Thakur, Rescigno, and Schafer (1972, 1973), and Thron (1972). Second, several authors have investigated problems of statistical inference for the transition rates in stochastic compartment models; see Burkinshaw and Marshall (1971), Cornfield, Steinfeld, and

Greenhouse (1970), Kodell and Matis (1976), Matis and Hartley (1972), Rodda et al. (1975), and Shah (1976). Last, the actual application of compartment models to biomedical, ecological, and chemical systems, as well as to pharmacokinetics, has been carried out, for example, by Metzler (1971), Rödenbeck et al. (1975), Sheppard (1962), Siegel, Cooper, and Meisner (1968) and Uppuluri and Bernard (1967). A large bibliography is given in Jacquez (1972).

The present paper falls into the first category: we suggest a new approach to stochastic compartment analysis based on mathematical <u>diffusion processes</u>; see Feller (1971) for an introduction, and Arnold (1973) and Gikhman and Skorohod (1971) for a systematic treatment. In short, we write stochastic differential equations to describe compartment concentration changes, and show that in a natural limit interesting joint distributions are jointly Gaussian or Normal. In the literature a variety of different compartment models have been formulated for one up to n-compartment, reversible or irreversible, open or closed, systems. These have generally been characterized by discrete-valued state variables for compartment contents, the latter changing according to multivariate birth-and-death processes. Kolmogorov forward equations for the transition probabilities are then derived, and solved by transforms.

Purdue (1974) notes the similarity of these models to those for infinite server queues. We develop and discuss this connection in the appendix of this paper. For such discrete models it is possible to write down expressions for the moments of compartment contents at

a fixed time; under certain conditions (Poisson inputs, transition rates depend linearly on compartment contents) the contents of the compartments are statistically independent and Poisson distributed. Cardenas and Matis (1975a,b) have extensively investigated such models. The approach taken here, that of replacing a discrete birth and death process with a continuous diffusion, is approximate. However, the results agree with the exact solution in the case of linear transition rates up to second moments. Furthermore, the limiting process may be shown rigorously to be normal, allowing the use of statistical inference procedures validated for normal distributions and processes. Perhaps more important is the fact that the diffusion approximation applies to situations with nonlinear transition Michaelis-Menten-type rates, where "exact" discrete-state methods yield cumbersome results; see McNeil and Schach (1973) for various examples concerning populations. It is reassuring to find that the diffusion approximations often agree exceptionally well with the birth and death solution; see Gaver and Lehoczky (1975,1976) for numerical comparisons.

2. A Model

We consider a general n-compartment model with time-dependent transition rates. Let $C_i(t)$, $i = 1,\ldots,n$ represent the contents of compartments $1,\ldots,n$ respectively at time t. We assume that the state of the system $\underset{\sim}{C}(t) = (C_1(t),\ldots,C_n(t))$ is a Markov process with transition probabilities given by

$$P(\Delta_i(t)=1,\ \Delta_j(t)=0,\ j\neq i\,|\,\underset{\sim}{C}(t)) = N\lambda_{0i}(t)dt + o(dt) \qquad i = 1,\ldots,n$$

$$P(\Delta_i(t)=-1,\ \Delta_j(t)=0,\ j\neq i\,|\,\underset{\sim}{C}(t)) = \lambda_{i0}(t)\ C_i(t)dt + o(dt) \qquad i = 1,\ldots,n \tag{1}$$

$$P(\Delta_i(t)=-1,\ \Delta_j(t)=+1,\ \Delta_k(t)=0,\ k\neq i,j\,|\,\underset{\sim}{C}(t)) = \lambda_{ij}(t)\ C_i(t)dt + o(dt)$$

$$\text{for } 1 \le i,\ j \le n,\ i\neq j,\ \lambda_{ij} \ge 0 .$$

where $\Delta_i(t) = C_i(t + dt) - C_i(t)$, and N is a parameter that can be thought of as a dose level, eventually allowed to be large.

The first of the three transition probabilities represents an increase in compartment i of size 1 from the outside. The second represents a decrease in compartment i of size 1 to the outside. Finally, the third represents a transfer of size 1 from compartment i to compartment j.

The above formulation is rather general, and allows many different compartment systems to be studied simultaneously. It allows for an open system if $\lambda_{0i}(t) > 0$ for some $i = 1,\ldots,n$ or a closed system if $\lambda_{0i}(t) = 0$ for $i = 1,m,n$. The flows can be either reversible if $\lambda_{ij}(t) > 0$ implies $\lambda_{ji}(t) > 0$ or irreversible if $\lambda_{ij}(t) > 0$ implies $\lambda_{ji}(t) = 0$.

We wish to study the case where $\sum_{i=1}^{n} C_i(t)$ is large, say proportional to some number N. A diffusion approximation arises when N becomes large and we expand $\underset{\sim}{C}(t)$ into terms of order N and $\sqrt{N}$. We can insure that $\sum_{i=1}^{n} C_i(t)$ is large in two different ways. For open systems we assume, as given in (1), that the transition probabilities into the system from the outside are themselves directly proportional to N. For closed systems where there is no input from the outside, we must assume that each compartment has contents proportional to N at time 0, that is $C_i(0) = Nc_i(0)$.

The effect of assuming $\sum_{i=1}^{n} C_i(t)$ to be proportional to N is that transitions of all types occur very frequently. As a result, in any short time interval there will be many transitions of each

type. Each type of transition represents a change of +1 or -1 in the contents of a certain compartment. In a short time interval the total change will be a sum of independent Bernoulli random variables, and, as such, normally distributed by virtue of the central limit theorem. Actually, much more is true. Focusing on the compartment process $\{\underset{\sim}{C}(t), t \geq 0\}$ over time rather than at a single fixed time we see that the process will have normally distributed increments and hence be Gaussian. This observation is the key to understanding the diffusion approximation approach. The mathematical development of this approach is not given here; see Kurtz (1971) and Barbour (1972), and the paper by Schach and McNeil (1973).

3. Mathematical Development

In this section we derive the diffusion approximation approach outlined above in a manner that seems intuitively appealing. The exposition will be in terms of (Ito-type) stochastic differential equations; although, as will appear subsequently, the stochastic differential equations describing stochastic variations in compartment contents are not ambiguous of interpretation. The derivation to be presented next is supplemented by further discussion, reserved for the Appendix, that relates the present theory to the approach by Barbour (1974), and also to infinite server queueing-type models.

Let, then, $dC_i(t) = C_i(t + dt) - C_i(t)$ represent the change in the contents of compartment i in time $(t, t + dt)$. The change $dC_i(t)$ may be viewed as a sum of independent random variables:

(a) inputs from outside the system, with mean and variance $N\lambda_{0i}(t)\, dt$;

(b) inputs from compartment j $(j \neq i)$, with mean and variance $\lambda_{ji}(t)\, C_j(t)\, dt$;

(c) outputs to compartment k $(k \neq i)$, with mean and variance $\lambda_{ik}(t)\, C_i(t)\, dt$;

(d) outputs from the system via compartment i, with mean and variance $\lambda_{i0}(t)\, C_i\, dt$.

Represent the change in contents of compartment i in the manner of diffusion, i.e. in terms of drift and diffusion terms:

$$dC_i(t) = [N\lambda_{0i}(t) - \sum_{\substack{j=1 \\ j\neq 1}}^{n} \lambda_{ij}(t)\, C_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} \lambda_{ji}\, C_j(t)]\, dt$$

$$+ \sqrt{N\lambda_{0i}}\, dW_{0i}(t) - \sum_{\substack{j=0 \\ j\neq i}}^{n} \sqrt{\lambda_{ij}(t)\, C_i(t)}\, dW_{ij}(t) \qquad (2)$$

$$+ \sum_{\substack{j=1 \\ j\neq i}}^{n} \sqrt{\lambda_{ji}(t)\, C_j(t)}\, dW_{ji}(t)$$

$i = 1,2,\ldots,n$; $\underset{\sim}{C}(0) = N\underset{\sim}{c}(0)$, and $\{W_{ij}(t),\ 0 \leq i, j \leq n,\ i \neq j\}$. is a family of standard Wiener processes, see Arnold (1974).

Expression (2) is motivated as follows: the drift term, in brackets, represents the expected change in $C_i(t)$ over (short) time interval $(t, t + dt)$, given the states of all compartments and the corresponding infinitesimal flow rates or transition probabilities. The remaining terms represent the various random components of change, modeled as Gaussian random variables; the latter is plausible as $N \to \infty$ on central limit theorem grounds. For instance, arrivals from outside the system in $(t, t + dt)$ are Poissonian, and hence for large N, nearly Gaussian, with mean and variance specified by (a) above, and this accounts for the first bracketed and unbracketed terms in (2).

It is shown in Kurtz (1971) that

$$\frac{C_i(t)}{N} \to c_i(t) \quad \text{as} \quad N \to \infty \quad \text{in probability;} \tag{3}$$

see also Barbour (1974). By analogy with the central limit theorem, consider the normalized process

$$X_i(t) = \frac{C_i(t) - Nc_i(t)}{\sqrt{N}}\ ; \tag{4}$$

hence express the concentration as

$$C_i(t) = Nc_i(t) + \sqrt{N}\, X_i(t)\ . \tag{5}$$

In matrix form, $\underset{\sim}{C}(t) = N\underset{\sim}{c}(t) + \sqrt{N}\,\underset{\sim}{X}(t)$.

The vector function $N\underset{\sim}{c}(t)$ is referred to as the deterministic approximation, and $\sqrt{N}\, X(t)$ is a stochastic noise process superimposed upon the deterministic approximation. It remains to characterize $\underset{\sim}{c}(t)$ and $\underset{\sim}{X}(t)$. The stochastic process $\underset{\sim}{X}(t) = (X_1(t), \ldots, X_n(t))$ defined by (4) satisfies a stochastic differential equation similar to (2), and it can be derived from (2) by an application of Ito's Lemma (Arnold, p. 90, or Gikhman and Skohorod, p. 24). The stochastic differential equation governing $X(t)$ is given by

$$d\underset{\sim}{X}(t) = \underset{\sim}{A}(t)\, \underset{\sim}{X}(t)\, dt + \underset{\sim}{B}(t)\, d\underset{\sim}{W}(t) - \sqrt{N}\, (\underset{\sim}{c}'(t) - \lambda_0(t) - \underset{\sim}{A}(t)\, \underset{\sim}{c}(t))\, dt \qquad (6)$$

where

$$\underset{\sim}{A}(t) = a_{ij}(t)\ , \qquad 1 \leq i,\ j \leq n$$

with $a_{ij}(t) = \lambda_{ji}(t)$ for $i \neq j$, $a_{ii}(t) = - \sum_{\substack{j=0 \\ j\neq i}}^{n} \lambda_{ij}(t)$

$$\underset{\sim}{\lambda}_0(t) = (\lambda_{01}(t), \ldots, \lambda_{0n}(t))^T$$

$$\underset{\sim}{W}(t) = (W_{01}(t), \ldots, W_{0n}(t),\ W_{10}(t), \ldots, W_{n0}(t),\ W_{12}(t), \ldots, W_{1n}(t),\ \ldots,\ W_{n,n-1}(t))^T$$

$$\underset{\sim}{B}(t) = (b_{ik}(t)) \qquad 1 \leq i \leq n,\ 1 \leq k \leq n(n+1)$$

with

$$b_{ii}(t) = \sqrt{\lambda_{0i}(t)} \qquad i = 1,\ldots,n$$

$$b_{i(n+i)}(t) = -\sqrt{\lambda_{i0}(t)\, C_i(t)/N}$$

$$b_{i(2n+(i-1)(n-1)+j-1)}(t) = -b_{j(2n+(i-1)(n-1)+j-1)}(t)$$

$$= -\sqrt{\lambda_{ij}(t)\, C_i(t)/N}\,, \qquad j > i$$

$$b_{i(2n+(i-1)(n-1)+j)}(t) = -b_{j(2n+(i-1)(n-1)+j)}(t)$$

$$= -\sqrt{\lambda_{ij}(t)\, C_i(t)/N}\,, \qquad j < i$$

and all other $b_{ik} = 0$.

We now let $N \to +\infty$ in (6). First, the terms in $B(t)$ involving $\sqrt{\lambda_{ij}(t)\, C_i(t)/N}$ converge to $\sqrt{\lambda_{ij}(t)\, c_i(t)}$. Second, equation (6) contains a term proportional to N. The coefficient of this term must be identically 0 for all $t \geq 0$ or (6) will not converge to a finite limit. Consequently $\underset{\sim}{c}(t)$ must satisfy

$$\underset{\sim}{c}'(t) = \underset{\sim}{\lambda}_0(t) + \underset{\sim}{A}(t)\, \underset{\sim}{c}(t) \qquad (7)$$

and, given that $\underset{\sim}{c}(t)$ satisfies (7), equation (6) becomes

$$d\underset{\sim}{X}(t) = \underset{\sim}{A}(t)\, \underset{\sim}{X}(t) + \underset{\sim}{B}(t)\, d\underset{\sim}{W}(t) \qquad (8)$$

where $C_i(t)/N$ terms are replaced by $c_i(t)$ in $\underset{\sim}{B}(t)$. Note that the modelling ambiguity sometimes associated with stochastic differential equation representations, see Arnold (1973), Chap. 10, does not arise because the diffusion coefficient, $B(\cdot)$, of (8) does not involve $\underset{\sim}{X}$.

The deterministic approximation to $\underset{\sim}{C}(t)$ is given by $N\underset{\sim}{c}(t)$ where $\underset{\sim}{c}(t)$ is characterized by (7). This system of differential equations is stable in the sense of Liapunov because all eigenvalues of $\underset{\sim}{A}(t)$ have strictly negative real parts. The stochastic noise process superimposed on the deterministic approximation is given by $\sqrt{N}\underset{\sim}{X}(t)$ where $\underset{\sim}{X}(t)$ is characterized by (8). The stochastic differential equation given by (8) describes a <u>nonstationary multivariate Ornstein-Uhlenbeck process</u>. Much is known about such processes, see Arnold (1974); we will return to a discussion of the noise process in a later section.

4. The Deterministic Approximation

The system of differential equations given in (7) along with an initial configuration $\underset{\sim}{c}(0)$ can be easily solved. If $\underset{\sim}{\lambda}_0(t) = \underset{\sim}{0}$, the closed system case, then

$$\underset{\sim}{c}(t) = \exp\left(\int_0^t \underset{\sim}{A}(s)ds\right)\cdot\underset{\sim}{c}(0) \qquad (9)$$

where $\exp(\underset{\sim}{M}) = I + M + M^2/2! + \cdots$ for any square matrix $\underset{\sim}{M}$. For the open system, nonhomogeneous, case with $\underset{\sim}{\lambda}_0(t) \neq 0$ one first multiplies by $\exp(-\int_0^t \underset{\sim}{A}(s)ds)$ to obtain

$$\frac{d}{dt}\left(\exp\left(-\int_0^t \underset{\sim}{A}(s)ds\right)\cdot\underset{\sim}{c}(t)\right) = \exp\left(-\int_0^t \underset{\sim}{A}(s)ds\right)\cdot\underset{\sim}{\lambda}_0(t) \quad . \qquad (10)$$

This equation can be integrated and the result multiplied by $\exp(\int_0^t \underset{\sim}{A}(s)ds)$ to give

$$\underset{\sim}{c}(t) = \int_0^t \exp(\int_u^t \underset{\sim}{A}(s)ds) \cdot \underset{\sim}{\lambda}_0(u)du + \exp(\int_0^t \underset{\sim}{A}(s)ds) \cdot \underset{\sim}{c}(0) \qquad (11)$$

Equation (11) provides a complete solution to the problem of describing $\underset{\sim}{c}(t)$. Simplifications are not possible in general; however, equation (11) can always be solved numerically by standard numerical integration techniques. We can consider a special case which allows equation (11) to be substantially simplified. Suppose we assume that all transition probabilities, $\lambda_{ij}(t)$, $1 \leq i \leq n$, $0 \leq j \leq n$, $i \neq j$, exhibit the same time dependence, or that $\lambda_{ij}(t) = \lambda_{ij} f(t)$ where $f(t)$ is some function of time. The matrix $\underset{\sim}{A}(t)$ now has the form

$$\underset{\sim}{A}(t) = \underset{\sim}{A} f(t) \qquad (12)$$

where

$$\underset{\sim}{A} = (a_{ij}) \quad \begin{cases} a_{ij} = \lambda_{ji} & j \neq i \\ a_{ii} = -\sum_{\substack{j=0 \\ j \neq i}}^{n} \lambda_{ij} & \end{cases}$$

Assume that $\underset{\sim}{A}$ can be diagonalized and has eigenvalues $\theta_1, \theta_2, \ldots, \theta_n$, left eigenvectors $\underset{\sim}{\ell}_1, \ldots, \underset{\sim}{\ell}_n$, and right eigenvectors $\underset{\sim}{r}_1, \ldots, \underset{\sim}{r}_n$. This gives

$$A(t) = RD(t)L \quad \text{with} \quad LR = I \tag{13}$$

where $R = (r_1, r_2, \ldots, r_n)$, $L = (\ell_1, \ldots, \ell_n)'$, and $D(t)$ is a diagonal matrix with ith entry $\theta_i f(t)$. Equation (13) can be integrated to give

$$\int_u^t A(s)ds = RF(u,t)L \tag{14}$$

with $F(u,t)$ a diagonal matrix having elements $(\theta_i \int_u^t f(s)ds)$. Finally (14) can be exponentiated to give

$$\exp \int_u^t A(s)ds = RG(u,t)L \tag{15}$$

where $G(u,t)$ is a diagonal matrix with the ith diagonal element $\exp(\theta_i \int_u^t f(s)ds)$. Equation (15) can be plugged back into (11) to give

$$c(t) = R\int_0^t G(u,t)\cdot L\cdot \lambda_0(u)du + RG(0,t)L\cdot c(0) \tag{16}$$

We illustrate the use of (16) by considering an example discussed by Cardenas and Matis (1975a). In that paper the authors consider a case with time-dependent transitions for a closed two-compartment system. For closed systems $\lambda_0(u) = 0$ and only the second term of (16) need be calculated. In this case it is assumed that

$$\lambda_{01}(t) = \lambda_{02}(t) = 0 \ ,$$
$$\lambda_{12}(t) = .3/(t+1),$$
$$\lambda_{10}(t) = .5/(t+1),$$
$$\lambda_{21}(t) = .4/(t+1) \ ,$$
and
$$\lambda_{20}(t) = .6/(t+1) \ .$$

$$A(s) = \begin{pmatrix} -.8 & .4 & \frac{1}{s+1} \\ .3 & -1 & \end{pmatrix}$$

and

$$A = \begin{pmatrix} -.8 & .4 \\ .3 & -1 \end{pmatrix}, \quad f(s) = \frac{1}{s+1} \ .$$

The matrix $\underset{\sim}{A}$ has eigenvalues $\theta_1 = -.9 + \sqrt{.13}$, $\theta_2 = -.9 - \sqrt{.13}$. Also $\exp(\theta_i \int_0^t f(s)ds) = (1+t)^{\theta_i}$. It is easy to calculate

$$\underset{\sim}{c}(t) = \begin{pmatrix} 1 & 1 \\ a/4 & b/4 \end{pmatrix} \begin{pmatrix} (1+t)^{\theta_1} & 0 \\ 0 & (1+t)^{\theta_2} \end{pmatrix} \begin{pmatrix} .12/(.12+a^2) & .4a/(.12+a^2) \\ .12/(.12+b^2) & .4b/(.12+b^2) \end{pmatrix} \cdot \underset{\sim}{c}(0$$

$$a = -.1 + \sqrt{.13} \tag{17}$$

$$b = -.1 - \sqrt{.13}$$

Equation (17) may be expanded to yield

$$c_1(t) = (.6386750491c_1(0) + .5547001962c_2(0))\,(1+t)^{\theta_1}$$
$$+ (.361324909c_1(0) - .5547001962c_2(0))\,(1+t)^{\theta_2}$$
$$c_2(t) = (.4160251472c_1(0) + .3613249509c_2(0))\,(1+t)^{\theta_1} \tag{18}$$
$$+ (-.4160251472c_1(0) + .6386750491c_2(0))\,(1+t)^{\theta_2}$$

with

$$\theta_1 = -\ .5394448725$$
$$\theta_2 = -1.2605551275$$

Transition probabilities for this model were approximated by Cardenas and Matis using a truncated infinite series approach. These transition probabilities can be derived directly from (18) by establishing appropriate initial conditions. For example, by setting $c_1(0) = 1$, $c_2(0) = 0$, $c_1(t)$ and $c_2(t)$ become $p_{11}(t)$ and $p_{12}(t)$, respectively. By setting $c_1(0) = 0$, $c_2(0) = 1$, $c_1(t)$ and $c_2(t)$ become $p_{21}(t)$ and $p_{22}(t)$, respectively. The results derived from (18) are compared with the approximations of Cardenas and Matis in Table 1. These results illustrate the accuracy of the deterministic approximations in (18), since the two answers agree to at least 8 significant figures. Furthermore, the numbers derived from (18) always exceed the Cardenas and Matis results. This is reasonable since the latter approximation is derived by truncation and is hence an underestimate of the true value.

The results in (18) illustrate another very important point. Compartment modelling has been criticized because it only allows levels which are mixtures of exponentials in t when, in fact, these models often do not fit data well (See Marcus (1975) p. 339 and Matis (1972). Much more complicated functions are required to give adequate fits including gamma, Pareto, Pareto-exponential, and first passage density functions. One can see that all of these types of functions can be produced by appropriate choice of $f(t)$. Mixtures of exponentials arise when $f(t) \equiv 1$; however, an enormous class of level functions can be produced by varying choices of $f(t)$. The introduction of time dependent transitions not only adds realism but produces models which can fit real data sets.

	t	Equation (18)	Cardenas and Matis 4-term approximation
	1	.5902421829	.5902421826
	2	.4435620915	.4435620872
$P_{11}(t)$	3	.3652902915	.3652902729
	4	.3155676392	.3155675836
	5	.2807030964	.2807029846
	1	.5151767471	.5151767467
	2	.3596617846	.3596617805
$P_{22}(t)$	3	.2823115397	.2823115195
	4	.2356325933	.2356325396
	5	.2041834275	.2041833201
	1	.1501308716	.1501308715
	2	.1678006137	.1678006133
$P_{21}(t)$	3	.1659575075	.1659575068
	4	.1598700918	.1598700879
	5	.1530393378	.1530393292
	1	.1125981537	.1125981539
	2	.1258504603	.1258504600
$P_{12}(t)$	3	.1244681306	.1244681301
	4	.1199025689	.1199025659
	5	.1147795033	.1147794969

TABLE 1: A Comparison of the Deterministic Approximation (18) with the Cardenas and Matis Four Term Approximation.

5. The Noise Process

The stochastic elements of the compartment process $\{\underset{\sim}{C}(t),\ t \geq 0\}$ are embodied in the nonstationary multivariate Ornstein-Uhlenbeck process described by (8). We summarize a few key results about such processes. These results are well known and available in Arnold, Section 8.2. First, we assume $\underset{\sim}{X}(0) = \underset{\sim}{0}$ that is the initial condition is nonstochastic and embodied in $\underset{\sim}{c}(0)$. The marginal distribution of $\underset{\sim}{X}(t)$ is

$$\underset{\sim}{X}(t) \sim \eta_n(\underset{\sim}{0}, \underset{\sim}{\Sigma}(t)) \tag{19}$$

that is an n-dimensional multivariate normal distribution where $\Sigma(t)$ is the unique nonnegative definite solution of the matrix Riccati equation

$$\underset{\sim}{\Sigma}'(t) = \underset{\sim}{A}(t)\ \underset{\sim}{\Sigma}(t) + \underset{\sim}{\Sigma}(t)\ \underset{\sim}{A}^T(t) + \underset{\sim}{B}(t)\ \underset{\sim}{B}^T(t) \tag{20}$$

Since $\underset{\sim}{C}(t) = N\underset{\sim}{c}(t) + \sqrt{N}\ \underset{\sim}{X}(t)$ we find

$$\underset{\sim}{C}(t) \sim \eta_n(N\underset{\sim}{c}(t),\ N\underset{\sim}{\Sigma}(t)) \tag{21}$$

Let $\underset{\sim}{B}(t)\ \underset{\sim}{B}^T(t) = \underset{\sim}{D}(t)$ and $\underset{\sim}{D}(t) = (d_{ij}(t))$ with

$$\begin{aligned} d_{ii}(t) &= (\lambda_{0i}(t) + \sum_{j=0}^{n} \lambda_{ij}(t)\ c_i(t) + \sum_{j=1}^{n} \lambda_{ji}(t)\ c_j(t)) \\ d_{ij}(t) &= -\ (\lambda_{ij}(t)\ c_i(t) + \lambda_{ji}(t)\ c_j(t)) \end{aligned} \tag{22}$$

The covariance matrix $\underset{\sim}{\Sigma}(t)$ can be calculated by various numerical methods applied to (20). We illustrate the calculation in the case $n = 2$ studied by Cardenas and Matis.

$$\underset{\sim}{A}(t) = \begin{pmatrix} -(\lambda_{10}(t)+\lambda_{12}(t)) & \lambda_{21}(t) \\ \lambda_{12}(t) & -(\lambda_{20}(t)+\lambda_{21}(t)) \end{pmatrix}$$

$$\underset{\sim}{\Sigma}(t) = \begin{pmatrix} \sigma_{11}(t) & \sigma_{12}(t) \\ \sigma_{12}(t) & \sigma_{22}(t) \end{pmatrix}$$

Equation (20) becomes

$$\dot{\underset{\sim}{s}}(t) = \underset{\sim}{G}(t)\ \underset{\sim}{s}(t) + \underset{\sim}{H}(t) \tag{23}$$

where

$$\underset{\sim}{s}(t) = (\sigma_{11}(t),\ \sigma_{12}(t),\ \sigma_{22}(t))'$$

$$\underset{\sim}{G}(t)$$

$$= \begin{pmatrix} -2(\lambda_{10}(t)+\lambda_{12}(t)) & 2\lambda_{21}(t) & 0 \\ \lambda_{12}(t) & -(\lambda_{10}(t)+\lambda_{20}(t)+\lambda_{12}(t)+\lambda_{21}(t)) & \lambda_{21}(t) \\ 0 & 2\lambda_{12}(t) & -2(\lambda_{20}(t)+\lambda_{21}(t)) \end{pmatrix}$$

$$\underset{\sim}{H}(t) = \begin{pmatrix} \lambda_{01}(t) + (\lambda_{10}(t) + \lambda_{12}(t)c_1(t) + \lambda_{21}(t)c_2(t)) \\ -(\lambda_{12}(t)c_1(t) + \lambda_{21}(t)c_2(t)) \\ \lambda_{02}(t) + \lambda_{12}(t)c_1(t) + (\lambda_{20}(t) + \lambda_{21}(t)c_2(t)) \end{pmatrix}.$$

Equation (23) can be solved in exactly the same manner as (7) with initial conditions $\underset{\sim}{s}(0) = \underset{\sim}{0}$, that is $\underset{\sim}{C}(0)$ is deterministic. We find

$$\underset{\sim}{s}(t) = \int_0^t \exp\left(\int_u^t \underset{\sim}{G}(s)ds\right)\cdot \underset{\sim}{H}(u)du \, . \tag{24}$$

For the case considered by Cardenas and Matis

$$\underset{\sim}{G}(t) = \frac{1}{1+t}\begin{pmatrix} -1.6 & .8 & 0 \\ .3 & -1.8 & .4 \\ 0 & .6 & -2 \end{pmatrix} + \frac{1}{1+t}\underset{\sim}{G} \, .$$

The matrix $\underset{\sim}{G}$ has eigenvalues ϕ_1, ϕ_2, ϕ_3 where

$$\phi_1 = 2\theta_1 = -1.978889745$$
$$\phi_2 = \theta_1 + \theta_2 = -1.8,$$
$$\phi_3 = 2\theta_2 = -2.521110255$$

$$\underset{\sim}{H}(u) = \begin{pmatrix} k_{11}(u+1)^{\theta_1 - 1} + k_{12}(u+1)^{\theta_2 - 1} \\ k_{21}(u+1)^{\theta_1 - 1} + k_{22}(u+1)^{\theta_2 - 1} \\ k_{31}(u+1)^{\theta_1 - 1} + k_{32}(u+1)^{\theta_2 - 1} \end{pmatrix}$$

where the k_{ij} coefficients are computing from (18). The other factor in the integrand is given by

$$\exp \int_u^t \underset{\sim}{G}(s)ds = \underset{\sim}{R}\begin{pmatrix} \left(\frac{1+t}{1+u}\right)^{\phi_1} & 0 & 0 \\ 0 & \left(\frac{1+t}{1+u}\right)^{\phi_2} & 0 \\ 0 & 0 & \left(\frac{1+t}{1+u}\right)^{\phi_3} \end{pmatrix}\underset{\sim}{L}$$

with

$$R = \begin{pmatrix} 1 & 1 & 1 \\ .6513878188 & -.25 & -1.151387819 \\ .4243060905 & -.75 & 1.32569391 \end{pmatrix}$$

$$L = \begin{pmatrix} .407957184 & .7085463502 & .3076923077 \\ .4615384615 & -.3076923077 & -.6153846153 \\ .1305557202 & -.4998540425 & 1 \end{pmatrix}$$

$\underset{\sim}{s}(t)$ can now be easily found. Each of the three variance-covariance terms is a linear combination of terms of the form

$$(1+t)^{\phi_i}((1+t)^{\phi_j-\phi_i} - 1)/(\phi_j-\phi_i) .$$

The Ornstein Uhlenbeck process described by (8) also has a known covariance function $k(s,t) = \mathrm{Cov}(\underset{\sim}{X}(s), \underset{\sim}{X}(t))$. The function $k(s,t)$ is given by the equation (T denotes transpose)

$$k(s,t) = \underset{\sim}{\Phi}(s) \int_0^{\min(s,t)} \underset{\sim}{\Phi}^{-1}(u)\, \underset{\sim}{B}(u)\, \underset{\sim}{B}^T(u) (\underset{\sim}{\Phi}^{-1}(u))^T \, du\, \underset{\sim}{\Phi}^T(t) \qquad (25)$$

with

$$\underset{\sim}{\Phi}(u) = \exp(\int_0^u A(s)ds) .$$

We do not use the covariance function in this paper; however, this function is important in the development of a statistical analysis of data from a compartment model. One may have data, say readings of drug concentrations in the blood stream, and wish to

estimate the parameters of the model, the λ_{ij}'s. Given the data have a multivariate normal distribution, the likelihood function can be written and estimators derived. The papers of Hartley and Matis (1971) and Kodell and Matis (1976) provide analyses in special cases. The results of this paper indicate that these kinds of results can be carried much further into far more general compartment models.

6. Steady State

In the case $\underset{\sim}{\lambda}_0(t) \neq \underset{\sim}{0}$, an open system, the system will approach steady state if $\lambda_{ij}(t) \to \lambda_{ij}$ as $t \to +\infty$. Steady state is a condition whereby the probability distribution which describes the marginal distribution of the system becomes time homogeneous even though the actual contents of the compartments continue to vary according to (8). The steady-state solution for a simple example is described in the Appendix.

The process $\{\underset{\sim}{C}(t),\ t \geq 0\}$ in steady state can also be approximated by $N\underset{\sim}{c} + \sqrt{N}\,\underset{\sim}{X}(t)$ where

$$0 = \underset{\sim}{\lambda}_0 + \underset{\sim}{A}\underset{\sim}{c} \quad \text{or} \quad \underset{\sim}{c} = -\underset{\sim}{A}^{-1}\underset{\sim}{\lambda}_0 \tag{26}$$

and $\{\underset{\sim}{X}(t),\ t \geq 0\}$ satisfies

$$d\underset{\sim}{X}(t) = \underset{\sim}{A}\underset{\sim}{X}(t) + \underset{\sim}{B}\, d\underset{\sim}{W}(t) \tag{27}$$

a stationary multivariate Ornstein-Uhlenbeck process. This means that

$$\underset{\sim}{C}(t) \sim \mathcal{N}_n(-N\underset{\sim}{A}^{-1}\underset{\sim}{\lambda}_0,\ N\underset{\sim}{\Sigma}) \tag{28}$$

where $\underset{\sim}{\Sigma}$ is the unique nonnegative definition solution of

$$\underset{\sim}{A}\underset{\sim}{\Sigma} + \underset{\sim}{\Sigma}\underset{\sim}{A}^T = -\underset{\sim}{B}\underset{\sim}{B}^T\ . \tag{29}$$

As an illustration we consider a two compartment open system, either reversible or irreversible

$$\underset{\sim}{A} = \begin{pmatrix} -(\lambda_{10}+\lambda_{12}) & \lambda_{21} \\ 0 & -(\lambda_{20}+\lambda_{21}) \end{pmatrix}$$

$$\underset{\sim}{B}\underset{\sim}{B}^T = \begin{pmatrix} \lambda_{01}+(\lambda_{10}+\lambda_{12})c_1+\lambda_{21}c_2 \\ -(\lambda_{12}c_1+\lambda_{21}c_2) \\ \lambda_{02}+\lambda_{12}c_1+(\lambda_{20}+\lambda_{21})c_2 \end{pmatrix} \tag{30}$$

$$c = \frac{\begin{pmatrix} \lambda_{20}+\lambda_{21} & \lambda_{12} \\ \lambda_{21} & \lambda_{10}+\lambda_{12} \end{pmatrix}\begin{pmatrix} \lambda_{01} \\ \lambda_{02} \end{pmatrix}}{(\lambda_{20}+\lambda_{21})(\lambda_{10}+\lambda_{12})-\lambda_{12}\lambda_{21}}$$

$$\begin{pmatrix} \sigma_{11} \\ \sigma_{12} \\ \sigma_{22} \end{pmatrix} = \begin{pmatrix} 2(\lambda_{10}+\lambda_{12}) & 2\lambda_{21} & 0 \\ \lambda_{12} & (\lambda_{10}+\lambda_{20}+\lambda_{12}+\lambda_{21}) & -\lambda_{21} \\ 0 & -2\lambda_{12} & 2(\lambda_{20}+\lambda_{21}) \end{pmatrix}^{-1} \underset{\sim}{B}\underset{\sim}{B}' \qquad (31)$$

Equations (30) and (31) thus complete the description of the multivariate normal density given in (28). While the $n = 2$ case can be done in closed form, the general case can be easily solved by numerical methods.

7. Extension to Nonlinear Models

The technique of diffusion approximations outlined and applied to general linear compartment models in the previous section also provides a tractable approach to handling nonlinear models. The compartment modelling literature is vast and the area is still in rapid development. Nevertheless, papers involving a stochastic process approach assume a linear system, that is, one in which transition rates from i to j are proportional to the contents of the ith compartment. It is unlikely that real pharmacokinetic processes operate so simply. Rather, the transition rates are more likely to be complicated functions of the contents of several compartment levels, and of time. Such complicated models have not appeared in the literature, perhaps because they present serious mathematical intractabilities using the standard Kolmogorov forward equations analysis.

The method of diffusion approximations can effectively handle nonlinear transition rates. The deterministic approximation will be a system of nonlinear ordinary differential equations. This will only rarely be solvable in closed form. Nevertheless, the numerical solution of such systems is a standard topic in numerical analysis. The important observation is that the stochastic differential equation representing the noise process superimposed upon the deterministic process will be nonstationary but linear (often Ornstein-Uhlenbeck). This means that the diffusion approximation approach will yield analytic results for nonlinear systems, since many results are readily available for linear stochastic differential equations (see Arnold, Chapter 8). It is hoped that this approach will encourage pharmacokinetic researchers to consider introducing nonlinear models should an analysis of data indicate the need.

Two additional points should be made. First, the analysis presented can be easily carried out when the process is represented in terms of volume and concentration rather than in terms of total contents. Second, the method of diffusion approximations illustrates that the compartment system contents will have a marginal Gaussian distribution. As such, one is in a position to give a statistical analysis of such a system either to estimate transition rates or, indeed, to design an experiment to make proper inferences about such parameters.

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APPENDIX

The purpose of this appendix is to further justify the earlier analysis, in particular, equations (7) and (8) and their implications. We do this in certain tractable simple cases, namely, those of one and two components.

1. The Theory of Kurtz (1971) and of Barbour (1974).

In Section 2 of Barbour (1974), hereafter called B, assumptions are given that imply convergence of the sequence of processes

$$\underset{\sim}{y}_N(t) = \sqrt{N}\left(\frac{\underset{\sim}{C}_N(t)}{N} - \underset{\sim}{c}(t)\right) = \frac{\underset{\sim}{C}_N(t) - N\underset{\sim}{c}(t)}{\sqrt{N}}, \quad N = 1,2,3,\ldots, \tag{A-1}$$

to the diffusion $\underset{\sim}{y}(t)$, as $N \to \infty$ in $D(0,T)$, i.e. the space of all right-continuous functions with left-hand limits. Note that the $\underset{\sim}{y}(t)$ of B will turn out to be the same as our stochastic noise process $\underset{\sim}{X}(t)$. We shall verify these assumptions for illustrative cases.

First consider the sequence of continuous parameter Markov processes $\underset{\sim}{x}_N(t) = \underset{\sim}{C}_N(t)/N$ on $[0,T]$, where $\underset{\sim}{C}_N(t)$ is the many-compartment model whose transitions are described by our (1). Notice that the changes in $\underset{\sim}{x}_N(t)$ are of size 0, $\pm$ 1/N, and that the infinitesimal transition rates are of the form $N\lambda_{0i}$, and $N\lambda_{ij}(C_i(t)/N)$, as specified by (2.1,B). We now discuss the assumption and the Theorem K of B for these illustrative situations.

Single-Compartment Model. Let $\lambda_{01}(t) = \lambda_{01}$, and $\lambda_{10}(t) = \lambda_{10}$ constant and positive, and $n = 1$, which represents a single-compartment system.

It is easily seen that there is a unique function $\xi(t)$ satisfying, for $0 \leq t \leq T$, the natural deterministic equation, (2.2,B):

$$\xi'(t) = \lambda_{01} - \lambda_{10}\xi(t) \ . \tag{A-2}$$

The solution is, putting $\xi(0) = c(0)$,

$$\xi(t) = c(0)e^{-\lambda_{10}t} + \frac{\lambda_{01}}{\lambda_{10}}(1-e^{-\lambda_{10}t}) = \left(c(0) - \frac{\lambda_{01}}{\lambda_{10}}\right) e^{-\lambda_{10}t} + \frac{\lambda_{01}}{\lambda_{10}} \ , \tag{A-3}$$

which is unique; hence B's Assumption A is justified. Suppose $0 < c(0) < \lambda_{01}/\lambda_{10}$ for example; other cases may be treated in analogous fashion. Then, in the terminology of Barbour (1974),

$$S = \left[c(0),\ c(0)\ e^{-\lambda T} + \frac{\lambda_{01}}{\lambda_{10}}(1 - e^{-\lambda_{10}T}) \right] \tag{A-4}$$

and

$$S^{\varepsilon} = \left[c(0) - \varepsilon,\ c(0)\ e^{-\lambda T} + \frac{\lambda_{01}}{\lambda_{10}}(1-e^{-\lambda_{10}T}) + \varepsilon \right] , \tag{A-5}$$

where $0 < \varepsilon < c(0)$ suffices. Clearly the transition rates are multinomial within S^{ε}, and B's Assumption B is also justified. Now Theorem K follows, and implies that $\underset{\sim}{y}_N(t) = \sqrt{N}\,(\underset{\sim}{x}_N(t) - \xi(t))$ converges to the diffusion $\underset{\sim}{y}(t)$, $\underset{\sim}{y}(0) = 0$, with the characteristic

function $\Phi(\theta,t) = E[e^{i\theta y(t)}]$ satisfying the differential equation

$$\frac{\partial\Phi}{\partial t} = -\theta\lambda_{10}\frac{\partial\Phi}{\partial\theta} - \frac{1}{2}\theta^2[\lambda_{01} + \lambda_{10}\xi(t)]\Phi \tag{A-6}$$

recognizable as describing the Ornstein-Uhlenbeck process whose stochastic differential equation is

$$dy = -\lambda_{10}y\,dt + \sqrt{\lambda_{01} + \lambda_{10}\xi(t)}\,dW\ , \tag{A-7}$$

this being the same s.d.e. as that obeyed by our noise process X for the present setup. Hence the procedure leading to our equations (7) and (8) yields the same results as those rigorously established by Kurtz, adapted by Barbour.

Note, too, that a steady-state solution will exist: simply set $\xi' = 0$ in (A-2) to discover the deterministic component: $\xi(\infty) = \lambda_{01}/\lambda_{10}$. The stochastic noise has, from (A-6) or (A-7), variance equal to the mean, namely, $\lambda_{01}/\lambda_{10}$. Thus the steady-state compartment content is, according to our theory, approximately $\eta(N\lambda_{01}/\lambda_{10}, N\lambda_{01}/\lambda_{10})$, as N becomes large. This is in accord with the fact that the exact distribution is Poisson $(N\lambda_{01}/\lambda_{10})$, as is well-known, and shown again subsequently in this Appendix.

Two-Component Model. Here $\underset{\sim}{C}(t) = (C_1(t), C_2(t))$, the allowed transitions and rates are summarized below.

	Transitions	Transition Rates	
	$C_1(t), C_2(t) \to$		
a)	$C_1(t) + 1, C_2(t)$	$N\lambda_{01}$	
b)	$C_1(t) - 1, C_2(t)$	$N\lambda_{10}\left(\frac{C_1(t)}{N}\right)$	(A-8)
c)	$C_1(t) - 1, C_2(t) + 1$	$N\lambda_{12}\left(\frac{C_1(t)}{N}\right)$	
d)	$C_1(t)\ , \quad C_2(t) - 1$	$N\lambda_{20}\left(\frac{C_2(t)}{N}\right)$	

State scaling, as in (2.1,B) alters the $\pm$ 1 changes to $\pm$ 1/N. The function $\underset{\sim}{\xi}(t) = (\xi_1(t), \xi_2(t))$ satisfies the differential equations

$$\begin{aligned} \xi_1' &= \lambda_{01} - (\lambda_{10} + \lambda_{12})\xi_1 \\ \xi_2' &= \lambda_{12}\xi_1 - \lambda_{20}\xi_2 \end{aligned} \tag{A-9}$$

For simplicity, we have not allowed entries into compartment 2 from outside, and have also omitted back flow from compartment 2 to compartment 1. The two equations are readily solved to produce a unique solution for all $t \geq 0$:

$$\xi_1(t) = c_1(0)\exp[-(\lambda_{10} + \lambda_{12})t] + \frac{\lambda_{01}}{\lambda_{10} + \lambda_{12}}[1 - \exp(-(\lambda_{10} + \lambda_{12})t)]$$

$$\xi_2(t) = c_{20} \exp(-\lambda_{20}t) + \frac{\lambda_{01}}{\lambda_{10} + \lambda_{12}} \frac{\lambda_{12}}{\lambda_{20}} [1 - \exp(-\lambda_{20}t)]$$

$$+ \left[c_1(0) - \frac{\lambda_{01}}{\lambda_{10} + \lambda_{12}}\right] \frac{\lambda_{12}}{\lambda_{20} - (\lambda_{10} + \lambda_{12})}$$

$$\times [\exp(-(\lambda_{10} + \lambda_{12})t) - \exp(-\lambda_{20}t)] \qquad \text{(A-10)}$$

Thus Assumption A is satisfied, with $c_1(0), c_2(0) > 0$. Assumption B is also satisfied with

$$0 < \varepsilon \leq \min[\underline{\xi}_1(T), \underline{\xi}_2(T)] \qquad \text{(A-11)}$$

where

$$\bar{\xi}_i(T) = \min_{0 \leq t \leq T} \underline{\xi}_i(T) > 0, \quad i = 1,2;$$

It is clear from the differential equations that such values will always exist. Hence

$$\underset{\sim}{y}_N(t) = N^{1/2} \left(\frac{\underset{\sim}{C}_N(t)}{N} - \underset{\sim}{\xi}(t) \right)$$

converges weakly to a bivariate diffusion. Proceeding further, evaluate the characteristic function of the limiting noise,

$$E[\exp(i\theta_1 y_1(t) + i\theta_2 y_2(t))] = \Phi(\theta_1,\theta_2,t); \qquad \text{(A-12)}$$

The latter satisfies the following partial differential equation, from (2.7,B):

$$\Phi' = [-\theta_1\lambda_{10} + (-\theta_1 + \theta_2)\lambda_{12}]\Phi_{\theta_1} - \theta_2\lambda_{20}\Phi_{\theta_2}$$

$$- \frac{1}{2} [\theta_1^2\lambda_{01} + \theta_1^2\lambda_{10}\xi_1(t) + (-\theta_1+\theta_2)^2\lambda_{12}\xi_1(t) + \theta_2^2\lambda_{20}\xi_2(t)]\Phi \tag{A-13}$$

This is recognizable as describing a bivariate Ornstein-Uhlenbeck process. Now one may differentiate (A-13) at $\theta_1 = \theta_2 = 0$, utilizing the fact that

$$V_i(t) = E[y_i^2(t)] = -\Phi_{\theta_i\theta_i}(0,0,t), \quad i = 1,2,$$

and

$$V_{12}(t) = E[y_1(t)\ y_2(t)] = -\Phi_{\theta_1\theta_2}(0,0,t)$$

to derive differential equations for the elements of the variance-covariance matrix of y. Not surprisingly, these differential equations agree with (23) (with λ_{ij} constant, and, in this case, $\lambda_{21} = 0$), i.e., $V_1(t) = \sigma_{11}(t)$, $V_{12}(t) = \sigma_{12}(t)$, $V_2 = \sigma_{22}(t)$. Thus if the same initial conditions are adopted for $\underset{\sim}{\xi}$, $\underset{\sim}{c}$ and for $\underset{\sim}{y}$, and $\underset{\sim}{X}$ the deterministic and noise components of the approximations of this paper and of B are seen to be identical. The validation can be extended with no difficulty in principle to the general situation.

2. Relation to Infinite-Server and Linear Markov Population Models

The class of compartment models described by the transition scheme (1) are similar to the classical Poisson-arrival infinite-server models of queueing theory and identical to certain Markov population models of Bartlett (1949), and Kingman (1969). We now briefly explore the connection, illustrating by the single-compartment and two-compartment examples. In particular, it will be shown that, even in the time-dependent parameter case, limiting Gaussian marginal distributions occur for compartment contents, in agreement with the development of the paper.

Single-Compartment Model. Let $C_1(t,u)$ denote the number of arrivals to the system that have occurred in the time interval (u,t), $0 \leq u \leq t$, and that are present in compartment 1 at time t. Let $I_1(t,u)$ be the probability that an arrival occurring at time u is present in compartment 1 at time t. Consider the generating function of $C_1(t,u)$,

$$E[z_1^{C_1(t,u)}] = g(z_1,t;u) \tag{A-14}$$

Now by the assumption of Poissonian arrivals, see (1), we may write

$$g(z_1,t;u) = [z_1 I_1(t,u)N\lambda_{01}(u)du + 1 - I_1(t,u)N\lambda_{01}(u)du]\; g(z_1,t;u+du), \tag{A-15}$$

where the bracketted expression is the generating function of the contribution to $C_1(t,u)$ from arrivals during $(u, u + du)$; independence permits the multiplcation. Subtract $g(z_1,t;u + du)$ from both sides, divide by du, and let $du \to 0$. The differential equation

$$-\frac{dg(z_1,t;u)}{du} = g(z_1,t;u)\ [(z_1-1)\ I_1(t,u)\ N\lambda_{01}(u)du] \qquad \text{(A-16)}$$

results, the solution of which is, when u is set equal to zero,

$$g(z_1,t;0) = E[z_1^{C_1(t)}\ |C_1(0)=0] = \exp[(z_1-1)N\int_0^t I_1(t,u)\lambda_{01}(u)du]\ , \qquad \text{(A-17)}$$

the generating function of the Poisson distribution with mean $N\int_0^t I_1(t,u)\ \lambda_{01}(u)du$. It now follows immediately from the central limit theorem that the distribution of

$$X_1(t) = \frac{C_1(t) - N\int_0^t I_1(t,u)\ \lambda_{01}(u)du}{\sqrt{N}} \qquad \text{(A-18)}$$

converges weakly to the normal law with mean zero and variance $\int_0^t I_1(t,u)\ \lambda_{01}(u)du$. Furthermore, it is easy to verify that

$$\mathrm{Var}[y(t)] = \int_0^t I_1(t,u)\ \lambda_{01}du = \frac{\lambda_{01}}{\lambda_{10}}(1 - e^{-\lambda_{10}t})$$

when λ_{01} and λ_{10} are both constants, and $y(t)$ is the solution of the stochastic differential equation (A-7) which results from following the approximation program that is the topic of the paper; we start with $C_1(0) = 0$. Verification in the time-dependent parameter case is also possible, but is more difficult. Thus the correct marginal distribution is verifable directly for this, the simplest, case. With more labor the joint distribution at different times may be found using an extension of the technique.

Two-Compartment Model. Consider the generating function of $(C_1(t,u),\ C_2(t,u))$, denoted by $g(z_1,z_2,t;u)$. Then an argument analogous to that joint presented shows that g satisfies a differential equation, which when solved yields

$$g(z_1,z_2,t;0) = \exp[N\{(z_1-1)\int_0^t I_1(t,u)\ \lambda_{01}(u)du$$

$$+ (z_2-1)\int_0^t I_2(t,u)\ \lambda_{01}(u)du\}] \qquad \text{(A-19)}$$

implying that the contents of the two compartments are Poisson distributed at time t, and that $C_1(t)$ and $C_2(t)$ are independent. The same central limit theorem argument now shows joint normality as $N \to \infty$ in agreement with the claims of the body of the paper. Calculations omitted here show that the diffusion approximation produces first and second moments that agree with those of the Poisson input model above. In particular, the correlation term, σ_{12}, of (20) equals zero, signifying the independence that we noted in (A-19).